14 December 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

Tecartus (Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured)
Treatment of mantle cell lymphoma
EU/3/19/2220

Sponsor: Kite Pharma EU B.V.

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Table of contents

1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured
Other name(s)	KTE-X19, autologous anti CD19 transduced CD3+ cells
International Non-Proprietary Name	-
Tradename	Tecartus
Orphan condition	Treatment of mantle cell lymphoma
Sponsor's details:	Kite Pharma EU B.V. Science Park 408 1098 XH Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Kite Pharma EU B.V.
COMP opinion date	16 October 2019
EC decision date	13 November 2019
EC registration number	EU/3/19/2220
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	J. Mueller-Berghaus, R. Kjeken
Applicant	Kite Pharma EU B.V.
Application submission date	9 January 2020
Procedure start date	28 January 2020
Procedure number	EMA/H/C/005102
Invented name	Tecartus
Proposed therapeutic indication	Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. Further information on Tecartus can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Tecartus
CHMP opinion date	15 October 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	M. E. Kalland, F. Naumann-Winter
Sponsor's report submission date	3 February 2020
COMP opinion (adoption via WP) date	20 October 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

The sponsor Kite Pharma EU B.V. submitted on 17 July 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured for treatment of mantle cell lymphoma (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured was considered justified based on preliminary clinical data showing favourable survival in patients with mantle cell lymphoma that relapsed after, or were refractory to, several lines of previous treatments;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. Median survival is 3 to 5 years;
- the condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improved survival in patients who relapsed from several lines of previous standard of care treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin's lymphoma. It constitutes 5–7% of malignant lymphoma in Western Europe (Dreyling, Ann Oncol. 2017; 28(S4): iv62–71). The entity is also included in the latest WHO classification of haematological malignancies from 2016 (Swerdlow, Blood 2016; 127(20): 2375-2390).

It is a B-cell malignancy with a broad spectrum of clinical, pathological, and biological features. Historically, the identification of the chromosomal translocation event t(11;14)(q13;q32) and the resulting cyclin D1 overexpression were of paramount importance in recognizing the clinical and biological diversity of this disease, but in addition to this constitutive dysregulation of the cell cycle, other mechanisms such as DNA damage response alterations and activation of cell survival pathways are integrated to drive MCL pathogenesis (Jares, J Clin Invest. 2012; 122(10): 3416-23).

The first sign of the condition is often painless swelling in the neck, armpit or groin, caused by enlarged lymph nodes. Other symptoms may include night sweats, unexplained high temperatures, and weight loss. The diagnosis of MCL is obtained by lymph node biopsy and bone marrow aspiration. Circulating MCL cells can be either detected by peripheral blood smear or flow cytometry. Generalised lymphoadenopathy and extranodal disease are relatively common. Extranodal disease may include bowel involvement (lymphomatoid polyposis). MCL is more common in men than in women with a ratio of around 3:1. The median age at diagnosis is 68 years.

The therapeutic indication proposed for marketing authorization "*Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor*" falls within the scope of the designated orphan condition "treatment of mantle cell lymphoma".

Intention to diagnose, prevent or treat

The medical plausibility is accepted based on the positive benefit/risk assessment of the CAT/CHMP.

Chronically debilitating and/or life-threatening nature

Since the designation of Tecartus as an orphan drug for the treatment of MCL (13 November 2019), there have been no changes in the chronically debilitating or life-threatening nature of the condition and no new therapies have improved the morbidity or mortality of MCL.

The COMP has previously acknowledged that the condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. The majority of patients will relapse, with median overall survival (OS) of around 10-13 months in patients who have progressed after chemotherapy and treatment with approved targeted agents.

Number of people affected or at risk

There have been no significant changes in the prevalence of the condition.

The sponsor performed a review of epidemiological data to estimate the prevalence of MCL and concluded on a 10-year prevalence estimate of 0.52 per 10,000 people in the EU in 2018. That proposed estimate is based on data from only one source, namely the CancerMPact (EU5: Germany, Italy, Spain, France, and the UK; 2008-2018 data). Epidemiological data on MCL covering the entire EU are not available. In addition, a search on PubMed/Google Scholar for peer-reviews articles reporting

MCL prevalence estimates was conducted, but no information on the result of this search was presented or used for the calculation of the prevalence estimate.

The proposed prevalence estimate is the same estimate as was proposed by the sponsor less than a year ago at the time of the orphan designation. It was then concluded that the condition was affecting around 0.6 in 10,000 persons in the EU, at the time the application was made. This estimate is considered acceptable.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Targeted therapies currently authorized in the community for the treatment of MCL include bortezomib (Velcade and generics) for newly diagnosed patients not candidates for SCT, and ibrutinib (Imbruvica), lenalidomide (Revlimid and generics), and temsirolimus (Torisel) for patients with r/r disease. There are also several medicinal products authorised at the national level for the treatment of the proposed condition, including doxorubicin, cyclophosphamide, vincristine, prednisolone, dexamethasone, bendamustine, fludarabine, mitoxantrone, etoposide, chlorambucil, procarbazine. An optimal sequence of treatments for relapsed or refractory (r/r) MCL has not been established. Choice of regimen is influenced by response duration to frontline therapy, comorbidities, tumour chemo-sensitivity, and overall risk-benefit evaluations.

Ibrutinib is authorised as a single agent for the treatment of adult patients with r/r MCL. No other treatment is specifically authorised for the treatment of patients relapsing from ibrutinib in third- or later lines of therapy.

According to the ESMO guidelines, the current standard of care for first-line treatment depends on the stage of MCL, the patients' age, clinical and biological risk factors, symptoms and tumour burden (Dreyling, Ann Oncol. 2017; 28(S4): iv62-71). First-line therapy often includes chemotherapy in combination with the CD20-targeting monoclonal antibody rituximab. Numerous combination regimens have been investigated, including R-CHOP (rituximab with cyclophosphamide, doxorubicin, vincristine and prednisone); R-CVP (rituximab with cyclophosphamide, vincristine and prednisone); rituximab with fludarabine and cyclophosphamide (R-FC); rituximab with bendamustine (BR); rituximab with cyclophosphamide, doxorubicin, bortezomib, and prednisone (VR-CAP); and rituximab with dexamethasone, cytarabine, and cisplatin (R-DHAP). Frontline therapy also includes autologous stem cell transplantation (SCT) therapy, mainly reserved for patients ≤ 65 years of age. Overall response rates (ORR) of up to 94% and complete response (CR) rates of up to around 40% have been achieved with first-line therapies. Despite high ORR, the majority of patients will relapse, and outcomes in the relapsed setting are much poorer. Recent studies have shown a median OS of 5 to 7 years in patients with earlier stages of disease, but median OS of approximately 10 to 13 months in patients who have progressed after chemotherapy and targeted agents.

In the r/r situation in MCL, the treatment concepts comprise immunochemotherapy followed by autologous/allogeneic SCT, Bruton's tyrosine kinase (BTK) inhibitors (ibrutinib and acalabrutinib; both approved in the US; only ibrutinib is approved in the EU), the immunomodulatory (and thalidomide analogue) agent lenalidomide, the m-TOR inhibitor temsirolimus and the BCL-2 antagonist venetoclax

(the latter not approved in the EU). Bortezomib is approved in the EU for use in combination with R-CHOP for the treatment of newly diagnosed MCL and has been investigated as a monotherapy in r/r MCL.

Responses to autologous SCT in relapse are inferior to those in first line and there is no consensus on the benefit of its use in r/r disease (Ketterer, Ann Oncol. 1997; 8(7): 701-4; Robinson, Leukemia 2015; 29(2): 464-73). By contrast, allogenic SCT has the potential to be curative in younger r/r MCL patients <65 years (Vose, Am J Hematol 2015; 90(8): 739-45), although few patients are candidates for this treatment due to the advanced age of most r/r MCL patients.

Significant benefit

The significant benefit of the proposed product is based on the beneficial effect in r/r MCL patients whose disease had relapsed or progressed on anthracycline- or bendamustine-containing chemotherapy regimens, an anti-CD20 antibody, and a BTK inhibitor.

The sponsor stated that the response rates observed in ZUMA-2 are unprecedented for subjects with r/r MCL who have progressive disease despite treatment with two or more previous systemic therapy regimens including a BTK inhibitor. A meta-analysis of the literature demonstrated that these patients have a pooled ORR of 28% (95% CI: 23, 34) to salvage therapies that are currently available. By contrast, ZUMA-2 demonstrated an ORR of 85% (95% CI: 75.0, 92.3) where 59% (95% CI: 47.4, 70.7) of the patients achieved a CR in the full analysis set (FAS; N=74 enrolled patients) after a single dose of KTE-X19. The lower bound of the ORR CI from the primary analysis set of ZUMA-2 is markedly higher than the upper bound of the 95% CI reported for the meta-analysis (34%).

The duration of the anti-tumour responses (DOR), especially for the cohort achieving CRs, compares favourably to the DOR reported in the historical cohort and is suggestive of a potential for long-term remission. This is consistent with the results from the secondary endpoints, which compares favourably to that reported in the literature, although median PFS and OS have not been reached. In addition, for patients who have progressed after two or more lines of systemic therapy including a BTK inhibitor, there are no products specifically authorized, and the available clinical data for Tecartus support improved efficacy over available alternative treatment options.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 20 October 2020

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the condition is life-threatening and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. Median survival is 3 to 5 years;
- the prevalence of mantle cell lymphoma (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.6 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Tecartus is of significant benefit to those affected by the orphan condition still holds;
- the sponsor has provided clinical data that demonstrate clinically relevant rate of responses with Tecartus in heavily pretreated relapsed or refractory patients who had previously been exposed to a Bruton's tyrosine kinase inhibitor;
- for patients who have progressed after two or more lines of systemic therapy including a Bruton's tyrosine kinase inhibitor there are no products specifically authorised and the available clinical data for Tecartus support improved efficacy over available alternative treatment options.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Tecartus, Autologous peripheral blood T cells CD4 and CD8 selected and CD3 and CD28 activated transduced with retroviral vector expressing anti CD19 CD28/CD3-zeta chimeric antigen receptor and cultured for treatment of mantle cell lymphoma (EU/3/19/2220) is not removed from the Community Register of Orphan Medicinal Products.